

# Vessel Dilator Enhances Sodium and Water Excretion and Has Beneficial Hemodynamic Effects in Persons With Congestive Heart Failure

David L. Vesely, MD, PhD; John R. Dietz, PhD; James R. Parks, RN; Mohammad Baig, MD; Michael T. McCormick, RPh, MS; Guillermo Cintron, MD; Douglas D. Schocken, MD

**Background**—Vessel dilator, a 37–amino acid peptide hormone synthesized in the heart, enhances urine flow 4- to 12-fold and sodium excretion 3- to 6-fold in healthy humans. The present investigation was designed to determine whether vessel dilator might have similar beneficial effects in persons with congestive heart failure (CHF).

**Methods and Results**—Vessel dilator (100 ng/kg body weight per minute) given intravenously for 60 minutes to NYHA class III CHF subjects increased urine flow 2- to 13-fold, which was still increased ( $P<0.001$ ) 3 hours after its infusion was stopped. Vessel dilator enhanced sodium excretion 3- to 4-fold in CHF subjects ( $P<0.01$ ), which was still significantly ( $P<0.01$ ) elevated 3 hours after infusion. Vessel dilator decreased systemic vascular resistance 24%, pulmonary vascular resistance 25%, pulmonary capillary wedge pressure 33%, and central venous pressure 27% while increasing cardiac output 34%, cardiac index 35%, and stroke volume index 24% without significantly affecting heart rate or pulmonary artery pressure in the CHF subjects. The control CHF patients did not have any changes in the above parameters.

**Conclusions**—These results indicate that vessel dilator has significant beneficial diuretic, natriuretic, and hemodynamic properties in humans with congestive heart failure. (*Circulation*. 1998;98:323-329.)

**Key Words:** natriuretic peptides ■ cardiac output ■ diuretics

Vessel dilator is a 37–amino acid peptide hormone synthesized primarily in the heart that enhances sodium and water excretion in both humans<sup>1</sup> and animals.<sup>2</sup> When examined in healthy humans, vessel dilator enhances urine flow 4- to 12-fold while increasing sodium excretion 3- to 6-fold.<sup>1</sup> In congestive heart failure (CHF), vessel dilator increases in the circulation in direct proportion to the amount of sodium and water retention, with persons with more severe CHF having significantly ( $P<0.001$ ) higher circulating concentrations than persons with mild CHF.<sup>3,4</sup> This increase in vessel dilator in the circulation is an apparent adaptive response by vessel dilator to overcome the sodium and water retention that characterizes CHF.<sup>3-6</sup> The present investigation was designed to determine whether vessel dilator has beneficial diuretic and natriuretic effects in humans with CHF. Evaluation of whether vessel dilator has beneficial hemodynamic effects on systemic vascular resistance, pulmonary vascular resistance, pulmonary capillary wedge pressure, central venous pressure, pulmonary artery pressure, cardiac output, stroke volume index, mean arterial pressure, and heart rate in CHF subjects was also performed.

## Methods

### CHF Volunteers

Twelve men at the James A. Haley Veterans Hospital with CHF (age, 33 to 72 years; average,  $58\pm 6$  years) were studied. These subjects

had heart rates ranging from 68 to 102 bpm, with respiration rates between 12 and 18 breaths per minute. These volunteers were divided into 2 similar groups; their ages, weights, blood pressures, and heart rates are shown in Table 1. Subjectively, all patients had a history of heart failure, including  $\geq 1$  of the following symptoms: dyspnea on mild exertion, paroxysmal nocturnal dyspnea, ankle swelling, or effort-related fatigue. Objectively, chronic left ventricular systolic dysfunction and dilatation were documented by cardiac catheterization, echocardiography, and/or radionuclide angiography. The left ventricular ejection fraction of each subject is listed in Table 1. Patients with a myocardial infarction within the preceding 6 months were excluded. All persons with renal failure and/or cirrhosis with ascites were also excluded. CHF was ischemic in nature in all the subjects except for control subject 4, whose was idiopathic. Each subject had NYHA class III CHF. Each subject had CHF for at least 6 months (range, 6 months to 3 years). All subjects in this study were in normal sinus rhythm with heart rates of  $\leq 102$  bpm (Table 1). Subjects with a creatinine level  $>1.5$  mg/dL were excluded because vessel dilator increases in the circulation of humans with renal failure.<sup>7,8</sup> Likewise, vessel dilator increases in the circulation of persons with ascites,<sup>9,10</sup> so these subjects were excluded from the present study. None of the patients' prescribed medications were taken the day of the study. If any prescribed medication had an evening dose, this dose was taken the evening before the study, but no medications were taken the day of the study. All over-the-counter medications were stopped at least 24 hours before the study. Specifically, nonsteroidals, including aspirin, were stopped 24 hours before the study because part of the natriuretic effects of vessel dilator are done by increasing the synthesis of prostaglandin E<sub>2</sub>, which in turn inhibits Na<sup>+</sup>-K<sup>+</sup>-ATPase in the kidney,<sup>11,12</sup> and

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From the Departments of Medicine, Physiology, and Biophysics, James A. Haley Veterans Hospital, and the University of South Florida Health Sciences Center, Tampa.

Correspondence to David L. Vesely, MD, PhD, Director, Atrial Natriuretic Peptides Research Laboratories, J.A. Haley Veterans Hospital-151, 13000 Bruce B. Downs Blvd, Tampa, FL 33612.

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**TABLE 1. Baseline Blood Pressure, Heart Rate, Age, Weight, Sodium, Potassium, and Left Ventricular Ejection Fraction of CHF Subjects Receiving Vessel Dilator**

	Age, y	Meds*	Weight, kg	Blood Pressure, mm Hg	Heart Rate, bpm	Na <sup>+</sup> , mmol/L	K <sup>+</sup> , mmol/L	EF, %
CHF controls								
1	70	V	89.1	116/76	96	131	3.86	38
2	63	V, D	79.6	101/57	80	134	4.12	15
3	42	V	95.5	125/71	88	133	4.59	23
4	35	V, D	84.0	144/90	98	137	4.77	20
5	75	V, D	84.0	117/54	83	136	4.68	26
6	64	V, D	93.2	107/50	72	137	4.45	28
Mean±SE	58±6		87.6±2.0	118/66±6/6	86±4	135±2	4.41±0.28	25±3
Vessel dilator								
1	56	V	86.4	142/74	82	136	4.28	35
2	57	D	89.0	122/73	102	129	3.60	13
3	64	D	70.9	118/75	82	139	4.30	14
4	72	V, D	89.1	98/53	68	131	3.70	20
5	72	V, D	77.3	146/76	96	137	5.00	10
6	52	V, D	89.0	114/68	74	134	4.32	14
Mean±SE	62±4		83.6±3.1	123/70±7/4	84±5	134±3	4.20±0.28	18±4

CHF indicates congestive heart failure; EF, ejection fraction; V, non-ACE vasodilator; and D, diuretic.

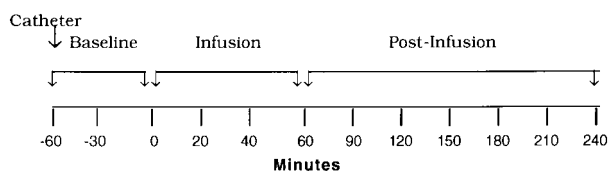
There was no significant difference in age, weight, blood pressure, heart rate, sodium, potassium, or medications between the 2 CHF groups when evaluated by 1-way ANOVA.

\*Meds indicates medications. All subjects were receiving digoxin and an ACE inhibitor, which were withheld the day of the study. In addition, some subjects were receiving non-ACE vasodilators or diuretics, which were withheld the day of the study.

nonsteroidals block this effect in vitro<sup>11,12</sup> and in vivo.<sup>13</sup> (Experimental subject 5, who stopped his ibuprofen 3 days before the study, revealed after the study was completed that he did take a 325-mg aspirin tablet the night before the study.) Each subject was receiving digoxin and an ACE inhibitor. In addition, many subjects were receiving another vasodilator or diuretic (see Table 1). Each subject was at dry weight. Informed consent was obtained from each volunteer after the nature and possible consequences of the studies were fully explained. This study was approved by the Institutional Review Board of the University of South Florida Health Sciences Center and the Research Committee of the James A. Haley Veterans Hospital. This study was also approved by the US Food and Drug Administration (FDA IND No. 32,119).

## Experimental Protocol

The experimental protocol is outlined in Figure 1. After written informed consent was obtained, an Insyte-w, 20-gauge, 1.5-in catheter was placed in 1 forearm of each subject for infusion, and an identical catheter was placed in the opposite forearm of each subject for blood sampling. A 60-minute baseline period preceded any infusion. A total volume of 20 mL of normal saline (0.9% sodium chloride, with or without vessel dilator) was infused by a constant-rate infusion pump over a 60-minute time period. Blood and urine samples were obtained every 20 minutes during the infusion and at



**Figure 1.** Experimental protocol. After a 60-minute baseline period, each human volunteer received 100 ng/kg body weight per minute venous infusion of vessel dilator or a 0.9% saline control for 60 minutes followed by a 3-hour postinfusion period, with urine and plasma samples obtained at each of the times on the lower portion of the graph.

30-minute time intervals during the 1-hour baseline and 3-hour postinfusion time periods. Urine volume was precisely measured with graduated cylinders. One hundred nanograms per kilogram of body weight per minute was chosen for the infusion dosage of vessel dilator because the rate of release of vessel dilator from the atrium of the heart with physiological stimuli is 138 ng/kg body weight per minute.<sup>14</sup> This is also the concentration shown to cause marked natriuresis and diuresis in healthy humans.<sup>1</sup> Molar equivalent of the 100-ng/kg body weight dose of vessel dilator is 26 pmol/kg body weight.

The subjects ingested their usual diets until the evening before the study. All subjects were studied in the morning after an overnight fast, beginning their baseline period at 8 AM. Each volunteer was studied while in the seated position. After completion of the 60-minute baseline period, to maintain a similar plasma volume throughout the study, water was given orally in milliliters for each milliliter of urine output at the above time periods. Each volunteer received only 1 vehicle or vessel dilator infusion.

## Purity of Vessel Dilator

The human form of vessel dilator was synthesized by Peninsula Laboratories. Before their use in these studies, samples of these commercially synthesized peptides were subjected to high-performance liquid chromatography to determine purity by use of a Novapak C<sub>18</sub> (5- $\mu$ m) cartridge column. The flow rate for the high-performance liquid chromatography study was 1 mL/min with 0.1% trifluoroacetate solvent in pump A and 60% acetonitrile in 0.1% trifluoroacetate in pump B, with a gradient of 0% to 60% acetonitrile achieved in 40 minutes. This evaluation verified purity and authenticity compared with the known high-performance liquid chromatography elution profile<sup>3</sup> of these peptides. After the respective peptides were determined to be pure, the peptides were dissolved in 0.9% saline solution in the hospital pharmacy, where pyrogen and sterility testing was performed before the 100-ng/kg body weight concentrations of each peptide were dispensed into two 10-mL syringes. Each 10-mL syringe was infused over a 30-minute time period. After the experiment was completed, the syringes and infusion catheter were examined by the radioimmunoassay described

below to determine the amount of the vessel dilator that may have remained within the syringes or tubing. Approximately 5% of vessel dilator remained on the walls of the syringes and tubing after completion of the infusion.

### Measurement of Vessel Dilator

The blood samples and flushings of the syringes and tubing with 4 mL of 0.9% sodium chloride were collected into chilled 5-mL EDTA tubes to prevent proteolytic breakdown of any peptides that might be present. Each sample was extracted with 100% ethanol (1:2 dilution).<sup>1,3</sup> Vessel dilator was measured by a radioimmunoassay devised to amino acids 31 to 67 of its 126-amino acid prohormone as described in detail previously by our laboratory.<sup>1,3,15</sup> The intra-assay coefficient of variation for the vessel dilator radioimmunoassay was 5.3%, and the interassay coefficient of variation was 8%. Serial dilution of pooled plasma has revealed excellent parallelism of standards and unknowns in this assay.<sup>3,16</sup>

### Measurement of Sodium, Potassium, Creatinine, and Osmolality

Sodium and potassium concentrations in the study were measured by flame photometry (Instrumentation Laboratory 943). Osmolality was measured by a micro-osmometer (Microosmett 5004, Precision Systems, Inc). Serum and urine creatinine were measured with a colorimetric diagnostic kit (Sigma Chemical Co) monitored at 500 nm. Creatinine clearance was calculated by multiplying the urine creatinine by the urine flow rate and dividing by the plasma creatinine. The creatinine clearance in this model system is a reflection of the glomerular filtration rate.

### Hemodynamic Response to Vessel Dilator

To determine whether the renal effects of vessel dilator administration were associated with changes in cardiac output or vascular tone, we evaluated the hemodynamic responses to vessel dilator infusion in the first 8 subjects with CHF (four of whom received vessel dilator and another 4 who received a placebo infusion of 20 mL of 0.9% sodium chloride during the experimental infusion phase). Under local anesthesia, a balloon-tipped, flow-directed catheter was placed percutaneously from a basilic vein in the arm to a final position in a branch of the pulmonary artery, confirmed by fluoroscopy. After catheter placement, there was a 1-hour lead-in stabilization phase. This was followed by the 1-hour infusion and 3-hour postinfusion data collection periods (Figure 1). Cuff blood pressure and ECG heart rate were obtained at 5-minute intervals. We recorded heart rate (beats per minute), systolic and diastolic blood pressures (millimeters of mercury), pulmonary artery pressure (millimeters of mercury), and capillary pulmonary wedge pressure (millimeters of mercury). Mean arterial pressure (millimeters of mercury) was estimated from the diastolic blood pressure plus one third of the difference between the systolic and diastolic blood pressures. Pulmonary artery pressure and pulmonary wedge pressure were obtained on a strip-chart recorder as both phasic and electronically dampened mean pressures, but for the purposes of this study, only the mean pressures are reported. Cardiac output was determined by the thermal dilution technique, in triplicate, by use of 10 mL of iced saline for each determination. Cardiac index was derived by correcting cardiac output for body surface area (liters per minute per square meter). Stroke volume index (millimeters per square meter) was obtained by dividing cardiac index by heart rate. Systemic and pulmonary vascular resistances were calculated by use of standard formulas<sup>17</sup> and are expressed as dynes per second per centimeter<sup>-5</sup>. Blood samples were obtained on completion of each phase for hematocrit, serum electrolytes, creatinine, osmolality, and measurement of vessel dilator. Timed, free-voiding urine collections were also obtained for volume, sodium, potassium, creatinine, and osmolality. After completion of the study, the catheters were immediately removed from the right side of the heart.

### Statistical Analysis

The data obtained in this investigation are given as mean±SE. Differences in measurements between subjects or groups of subjects were evaluated by one-way ANOVA. Measurements obtained in the same subject over time were evaluated by repeated-measures ANOVA. Maximum changes in systolic and diastolic blood pressures within groups were determined by a paired Student's *t* test. To be considered statistically significant, we required a probability value of  $P < 0.05$  (95% confidence limits).

### Results

Vessel dilator markedly increased urine volume and the urinary flow rate (Table 2) ( $P < 0.001$ ) of persons with CHF. At the end of the 60-minute infusion of vessel dilator, mean urinary flow had increased to  $7.55 \pm .75$  mL/min and was  $6.7 \pm .65$  mL/min 3 hours after its infusion was stopped, which were 4.8- and 4.3-fold higher than the baseline ( $1.56 \pm .35$  mL/min) urine flow in the CHF subjects (Table 2). Urinary flow did not increase significantly in the control CHF subjects during the combined 5-hour baseline and experimental periods (Table 2). Basal urine output and the increase in urine volume secondary to vessel dilator varied considerably among the individual CHF subjects (Table 2). In 5 of the 6 CHF individuals, urine volume was still significantly ( $P < 0.001$ ) increased 3 hours after the infusion of vessel dilator was stopped (Table 2). (The subject whose urine volume was not increased had taken a 325-mg aspirin tablet the night before the study.) One CHF subject (No. 3 experimental) who was studied for a longer period of time had increased urine volume and urine flow rate (2-fold) for 6 hours after his vessel dilator infusion was stopped.

The serum osmolality increased slightly but not significantly, while urine osmolality decreased significantly ( $P < 0.01$ ) secondary to the infusion of vessel dilator (Table 3). The urine osmolality of the CHF subjects not receiving vessel dilator tended to increase rather than decrease during the 5 hours of this investigation, but this increase did not reach significance (Table 3). In this result and results that follow, each individual also serves as his or her own control. The 60-minute time period referred to in the tables and figures (which is the time period immediately before 1 of the respective infusions was begun) serves as the control (baseline) value in the individual subjects with which one can compare any effects observed at later time points in this investigation. The diuresis, blood pressure decreases, and results of enhancing sodium excretion are the amount of decrease in blood pressure (or increase in sodium and water excretion) compared with the respective preinfusion measurement (ie, 60-minute time period) in each subject. The control group consisting of CHF individuals who received 20 mL of 0.9% saline (vehicle) has been added to demonstrate that hemodynamics, sodium, and water excretion do not change by chance alone during the time period used in this investigation.

Vessel dilator significantly ( $P < 0.01$ ) increased sodium excretion, with a doubling in sodium excretion occurring within 20 minutes (Table 3). Three hours after the vessel dilator infusion was stopped, sodium excretion was 3-fold greater than baseline sodium excretion (Table 3). The control subjects who received 0.9% saline did not have a significant

TABLE 2. Vessel Dilator Enhances Urine Volume in CHF Patients

	Infusion Time, min											
	0	30	60	80	100	120	150	180	210	240	270	300
CHF controls												
1	0	0	36	24	30	28	35	35	36	35	27	25
2	45	60	60	60	35	35	45	50	40	40	30	30
3	210	210	80	70	60	60	60	80	60	60	100	90
4	150	140	150	50	40	39	13	50	75	40	50	125
5	16	9	16	12	10	15	19	8	5	2	2	2
6	250	30	30	14	25	30	35	28	23	20	14	12
Mean±SE	112±43	75±34	62±20	38±10	33±7	35±6	35±7	42±10	40±10	40±10	37±14	47±20
Vessel dilator												
1	150	100	60	85	75	150	160	145	160	90	140	250
2	0	0	30	60	60	380	0	120	120	260	160	180
3	30	30	30	60	80	200	340	240	400	280	160	320
4	140	60	60	60	60	40	110	60	100	180	180	210
5	250	0	30	20	20	10	21	28	17	20	19	25
6	75	50	75	150	100	125	225	250	225	275	250	225
Mean±SE	107±37	60±40	47±8	73±18	66±11	151±54	143±52.4	141±37	170±54	184±44	152±31	202±40

CHF indicates congestive heart failure. Values are in milliliters. The zero-time urine reflects the amount in the bladder after overnight fasting. This value varied markedly from individual to individual, in part because some individuals voided at home before arriving for the study. The 1-hour baseline was thus used to ensure that each subject was at baseline. The 60-minute time period is each individual's own control time period for comparison of any increase in urine volume. Experimental subject 5 ingested a 325-mg aspirin tablet the night before the study, which may account for his diminished response to vessel dilator compared with the other experimental subjects. The enhancement of urine volume by vessel dilator was significant at  $P<0.01$  when evaluated by 1-way ANOVA.

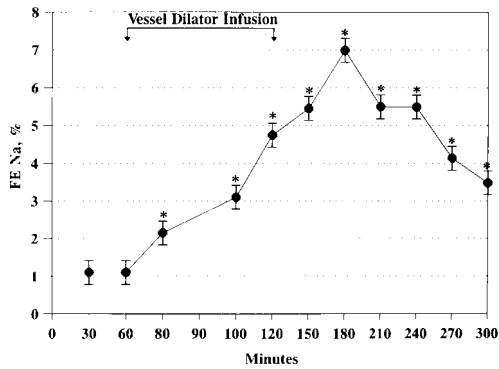
increase in sodium excretion (Table 3). Fractional excretion of sodium ( $FE_{Na}$ ) increased a maximum of 6-fold ( $P<0.001$ ) secondary to vessel dilator in the CHF subjects (Figure 2). Thus, the fractional excretion of sodium doubled 20 minutes after beginning the vessel dilator infusion and was 4.5-fold

greater than baseline at the end of the infusion (Figure 2). The fractional excretion of sodium peaked 1 hour after the vessel dilator infusion was stopped and was >3-fold above baseline ( $P<0.05$ ) 3 hours after cessation of the infusion (Figure 2). Vessel dilator did not significantly increase creatinine clear-

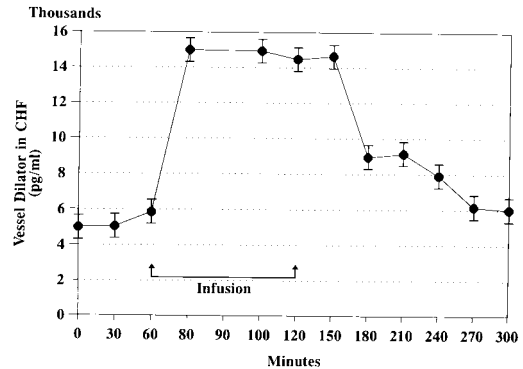
TABLE 3. Vessel Dilator Enhances Sodium Excretion in CHF Subjects

	Infusion Time, min										
	30	60	80	100	120	150	180	210	240	270	300
CHF controls											
1	...	24	16	19	15	8	7	29	17	3	1
2	192	198	220	114	119	53	63	18	4	7	36
3	169	149	168	162	163	152	124	164	128	193	186
4	473	695	342	120	132	165	53	317	167	665	567
5	10	22	20	18	21	23	10	4	2	2	2
6	119	134	93	136	120	172	139	111	95	56	45
Mean±SE	193±77	204±102	143±52	95±25	95±25	96±31	66±23	107±49	69±29	154±106	139±90
Vessel dilator											
1	123	128	357	236	360	192	203	234	387	312	350
2	...	112	220	240	540	...	273	262	139	147	182
3	117	106	165	104	210	340	176	240	159	101	139
4	99	95	209	169	180	302	275	297	221	188	391
5	...	26	68	67	34	47	58	42	45	39	57
6	190	104	195	125	138	159	208	171	213	195	168
Mean±SE	132±20	78±14	202±38	157±29	244±73	208±52	199±33	208±37	194±47	164±38	215±53

Values are  $\mu\text{Eq}$  of  $\text{Na}^+$  excreted per minute. There is no "zero" time value because this time period was after an overnight fast; some subjects had to void at home before arriving for the study, making the "zero" different for each individual. The true baseline for comparison of sodium excretion is the 60-minute time period (ie, immediately before the respective infusions). The congestive heart failure (CHF) controls received 20 mL of 0.9% saline (vehicle) infused during a 60-minute time period. Experimental subject 5 ingested a 325-mg aspirin tablet the night before the study, which may account for this individual's diminished response to vessel dilator compared with the other experimental subjects. The enhancement of sodium by vessel dilator was significant at  $P<0.01$  when evaluated by 1-way ANOVA.



**Figure 2.** Vessel dilator increases the fractional excretion of sodium ( $FE_{Na}$ ) in persons with congestive heart failure. \*Time points when filtration fraction of sodium was significantly ( $P < 0.05$ ) increased secondary to vessel dilator infusion at its 100 ng/kg body weight per minute concentration for 60 minutes when evaluated by repeated-measures ANOVA ( $n = 6$ ).

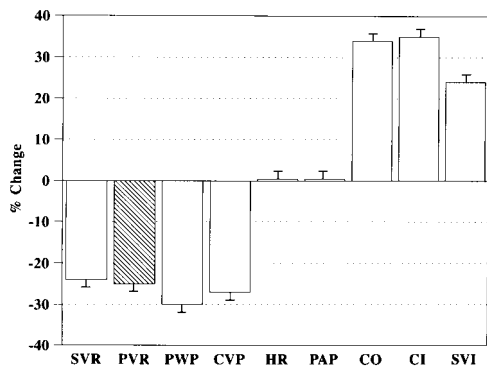


**Figure 4.** Increase in vessel dilator in the circulation with the infusion of 100 ng/kg body weight per minute for 60 minutes of vessel dilator in persons with congestive heart failure. Vessel dilator increased threefold ( $P < 0.01$ ) during the infusion and for 1/2 hour after the infusion was stopped; then it began to decrease, becoming not significantly different from baseline 2.5 hours after its infusion was ended when evaluated by ANOVA followed by Duncan's multiple range test (MRT). Infusion of vehicle ( $\Delta$ ) only (ie, 20 mL normal saline) did not cause the circulating concentration of vessel dilator to increase ( $n = 6$  for each group).

ance or glomerular filtration rate while increasing the filtration fraction of sodium.

Potassium and the fractional excretion of potassium ( $FE_{K^+}$ ) excretion did not significantly increase in the CHF subjects secondary to vessel dilator. Thus, potassium excretion remained stable throughout the vessel dilator infusion and during the 3 hours after infusion (data not shown). Serum sodium and potassium did not significantly change during the 5 hours of this investigation, with serum sodium and potassium never varying by more than 3 or 0.4 meq/L, respectively, from their baseline values (Table 1) in the CHF subjects who received vessel dilator or vehicle. Hematocrit increased  $3 \pm 1\%$  with vessel dilator infusion compared with no increase in the CHF subjects who received vehicle only.

During the vessel dilator infusion, systemic vascular resistance decreased 24% ( $P < 0.01$ ) from a mean of  $1127 \pm 18$  to  $857 \pm 16$  dynes  $\cdot$  s  $\cdot$  cm $^{-5}$  (Figure 3). Vessel dilator also decreased pulmonary vascular resistance 25% (ie, from



**Figure 3.** Systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), pulmonary capillary wedge pressure (PWP), and central venous pressure (CVP) decrease secondary to vessel dilator. Each of these decreases were significant at  $P < 0.05$  when evaluated by repeated-measures ANOVA, whereas no significant changes were found in heart rate (HR) or pulmonary artery pressure (PAP). Cardiac output (CO), cardiac index (CI), and stroke volume index (SVI) were significantly ( $P < 0.05$ ) increased when evaluated by repeated-measures ANOVA. There was no change in any of these parameters in the congestive heart failure subjects who received vehicle only ( $n = 4$  for each group).

$129 \pm 6$  to  $97 \pm 4$  dynes  $\cdot$  s  $\cdot$  cm $^{-5}$ ). Pulmonary capillary wedge pressure decreased 33% ( $21 \pm 3$  to  $14 \pm 3$  mm Hg), and central venous pressure decreased 27% ( $8.25 \pm 1.48$  to  $6.00 \pm 1.00$  mm Hg) in the subjects with CHF (all at  $P < 0.05$  or less). There was no significant change in heart rate or mean pulmonary artery pressure secondary to vessel dilator (Figure 3). Vessel dilator increased cardiac output 34% ( $5.35 \pm 0.9$  to  $7.9 \pm 1.2$  L/min). Cardiac index increased 35% ( $2.66 \pm 0.1$  to  $3.58 \pm 0.1$  L  $\cdot$  min $^{-1} \cdot$  m $^{-2}$ ) secondary to vessel dilator. Stroke volume index increased 24% ( $0.034 \pm 0.003$  to  $0.042 \pm 0.002$  mL/m $^2$ ) secondary to vessel dilator. Vessel dilator decreased systolic blood pressure  $15 \pm 6$  mm Hg in 4 of 6 CHF subjects and had no significant effect in 2 CHF subjects. Vessel dilator decreased diastolic blood pressure in each of the CHF subjects; the decrease in blood pressure averaged  $6 \pm 2$  mm Hg.

The measured basal circulating concentration of vessel dilator was increased threefold ( $P < 0.01$ ) in the CHF subjects compared with 54 healthy adults<sup>3</sup> (Figure 4). Infusion of vessel dilator increased the circulating concentration of vessel dilator another threefold ( $P < 0.01$ ) during its infusion (Figure 4). There were no side effects with the use of vessel dilator in CHF subjects.

### Discussion

Vessel dilator caused a significant diuresis in persons with CHF. The 2- to 13-fold increase in urine volume in the CHF subjects is nearly identical to the amount of diuresis (4- to 12-fold) found in healthy humans given vessel dilator,<sup>1</sup> suggesting that the effects of vessel dilator are not blunted in humans with CHF. Vessel dilator also stimulated a natriuresis (3- to 4-fold) in the human subjects with CHF that was similar to the amount of natriuresis previously observed in healthy human subjects secondary to vessel dilator.<sup>1</sup>

The ability of vessel dilator to increase the excretion of sodium and the filtration fraction of sodium ( $FE_{Na^+}$ ) without enhancing creatinine clearance or glomerular filtration rate

suggests that it is inhibiting the reabsorption of sodium in the renal tubules of persons with CHF. Vessel dilator is known to inhibit sodium reabsorption in the inner medullary collecting duct and renal tubules by inhibiting their  $\text{Na}^+\text{-K}^+\text{-ATPases}$  secondary to its ability to enhance the synthesis of prostaglandin  $\text{E}_2$ , which appears to be the final mediator of the inhibition of renal  $\text{Na}^+\text{-K}^+\text{-ATPase}$ .<sup>11,12</sup> Thus, the ability of vessel dilator to inhibit renal  $\text{Na}^+\text{-K}^+\text{-ATPase}$  appears intact in persons with CHF on the basis of its ability to enhance the excretion of sodium and the filtration fraction of sodium. Furthermore, the decreased natriuresis and diuresis of experimental subject 5, who ingested a 325-mg aspirin tablet (which blocks prostaglandin  $\text{E}_2$  synthesis) the night before the study compared with the other experimental subjects suggest that prostaglandin  $\text{E}_2$  synthesis secondary to vessel dilator<sup>11,12</sup> is very important in mediating the effects of vessel dilator in persons with CHF. Prostaglandin  $\text{E}_2$ -mediated natriuresis appears to act at other nephron segments in addition to the inner medullary collecting duct, including the thick ascending limb,<sup>18</sup> and it is possible that vessel dilator also affects this portion of the nephron, although this has not been determined experimentally yet.

The natriuretic and diuretic responses to vessel dilator in humans with CHF are similar to those found in an AV fistula model of high-output failure in dogs.<sup>19</sup> In the AV fistula high-output model of heart failure, the significant natriuretic and diuretic effects of vessel dilator were not blunted compared with its effects in healthy dogs, while the effects of atrial natriuretic factor were markedly blunted in the heart failure dogs compared with healthy dogs.<sup>19</sup> Likewise, the natriuretic and diuretic effects of atrial natriuretic factor in humans with CHF have been found to be blunted compared with healthy humans.<sup>20</sup>

The ability of vessel dilator to retain its beneficial effects in CHF persons while the effects of atrial natriuretic factor become blunted appears to be due to the ability of vessel dilator to enhance prostaglandin  $\text{E}_2$  synthesis in the kidney, which, in turn, inhibits renal  $\text{Na}^+\text{-K}^+\text{-ATPase}$ , resulting in a natriuresis.<sup>11,12</sup> Atrial natriuretic factor does not enhance the synthesis of prostaglandin  $\text{E}_2$  or have the ability to inhibit renal  $\text{Na}^+\text{-K}^+\text{-ATPase}$ .<sup>11,12</sup> The natriuretic property of vessel dilator in CHF subjects is especially impressive in light of the facts that (1) the natriuretic effects of vessel dilator are not blunted in CHF as found in the present investigation and (2) the natriuretic and diuretic effects of vessel dilator are at least equal to atrial natriuretic factor,<sup>1</sup> which has been found to be a more potent natriuretic and diuretic agent than furosemide in direct comparative studies.<sup>21</sup> The natriuresis and diuresis in most of the CHF subjects in the present investigation lasted at least 3 hours, suggesting that vessel dilator may be useful therapeutically for CHF in that its potent diuretic and natriuretic properties are sustained and long lasting.

The basal urine flow in the CHF subjects was 1.5 to 2 times higher than that of healthy individuals studied under identical conditions.<sup>1</sup> Thus, the water retention of CHF is not due to a decrease in the excretion of water because these subjects actually excrete more water than healthy individuals. This enhanced excretion of water in CHF individuals is most likely due to the endogenous increase of vessel dilator (and the other

atrial peptides) in CHF.<sup>3,4</sup> The finding that water excretion is increased in CHF subjects suggests that the endogenous increased synthesis<sup>22-24</sup> and release<sup>3,4</sup> of vessel dilator and the other atrial natriuretic peptides in CHF do have beneficial adaptive effects in CHF. The current observation that exogenous addition of vessel dilator increased water and sodium excretion of CHF subjects over and above that produced by endogenous atrial peptides suggests that part of the problem in CHF is that the heart does not produce enough vessel dilator and the other atrial peptides for the amount of sodium and water retention present. This phenomenon may play a role in the development and/or maintenance of CHF. Furthermore, the dramatic increase in water and sodium excretion when exogenous vessel dilator is added also suggests that the kidney is able to respond appropriately if enough vessel dilator reaches it, suggesting that the sodium and water retention of CHF may be reversible if one can either enhance atrial natriuretic peptide gene expression to increase synthesis of the atrial peptides, including vessel dilator, to a sufficient extent or add vessel dilator on a long-term (ie, daily) basis to eliminate sodium and water retention.

Vessel dilator was also found in the present investigation to have beneficial hemodynamic effects in persons with CHF. Vessel dilator decreased systemic vascular resistance and increased the cardiac index, which is a very beneficial effect in patients with CHF whose baseline state is characterized by increased systemic resistance and a reduced cardiac index. Vessel dilator also significantly decreased pulmonary vascular resistance, pulmonary capillary wedge pressure, and central venous pressure while simultaneously increasing cardiac output and systolic volume index. The hemodynamic effects of vessel dilator appear to be due in part to alteration of preload conditions of the heart as a result of a transmembrane fluid shift at the level of the capillary or venule with a reduction of venous volume and/or an increase of venous capacitance due to a direct venodilating effect. The hematocrit did increase secondary to vessel dilator, suggesting that a fluid shift was occurring. Vessel dilator is also known to be a potent venous dilator whose dilating effects do not require an intact endothelium and appear to be mediated via cGMP effects on the smooth muscle of blood vessels, including arterial (ie, aorta) smooth muscle.<sup>25</sup> Dilation of venous vessels decreases the capacitance of the venous system, resulting in decreased right atrial pressure. Because vessel dilator does decrease right atrial pressure in CHF,<sup>19</sup> this appears to be at least a partial cause of its beneficial hemodynamic effects in CHF.

The decrease in systemic vascular resistance secondary to the arterial vasodilation<sup>25</sup> of vessel dilator also decreases the backpressure on the heart, resulting in decreased left atrial pressure. Systemic blood pressure and systemic vascular resistance were decreased, suggesting afterload and preload improvement with vessel dilator. In CHF patients, when ventricular function is on the steep portion of the pressure-volume curve, preload reduction could decrease ventricular wall stress, producing an improvement in cardiac output, which indeed was found to increase in the present investigation. This hemodynamic response to vessel dilator appears

analogous in many respects to the responses evoked by pharmacological intervention with low-dose nitroglycerin (which is also mediated by cGMP) and/or loop diuretics.

In conclusion, the present study has identified 3 beneficial steady-state responses to vessel dilator in humans with congestive heart failure: (1) natriuresis, (2) diuresis, and (3) hemodynamic effects consistent with preload reduction caused by its vasodilating effect and possibly a transcapillary fluid shift, and after load reduction. The ability of vessel dilator to overcome the sodium and water retention of CHF suggests that it may be beneficial in treating persons with CHF. Further studies with vessel dilator of a larger population sample of CHF subjects are needed (1) to determine the ability of this peptide to cause beneficial effect in all classes of CHF subjects, (2) to determine the dose-response relationships of this peptide in CHF subjects, and (3) to further define the mechanism of action of vessel dilator in CHF subjects.

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